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LONG-TERM FOLLOW-UP AND COMPLICATIONS AFTER CARDIAC TRANSPLANTATION

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Cardiac transplantation has become an established therapy for cardiomyopathy and other irreversible cardiac diseases. Improvements in immunosuppression and management of infections has improved long-term survival following transplantation. The role of the primary care physician in the care of recipients will be expanding.

Transplant recipients receive close outpatient follow-up after discharge, primarily to monitor immunosuppression through laboratory evaluation and drug levels, monitor for rejection through endomyocardial biopsy, and to assess for any signs of opportunistic infection. The foundation for long-term immunosuppression is administration of cyclosporin, azathioprine and corticosteroids. Antibiotic prophylaxis is used to decrease the chance of infection with cytomegalovirus, *Pneumocystis, Candida, Toxoplasma,* and other opportunistic organisms. The major long-term complications include rejection, infection, hypertension, renal dysfunction, lipid abnormalities, and accelerated coronary atherosclerosis.

This review provides an overview of the short- and long-term follow-up of the cardiac transplant recipient, including routine care as well as detection and management of the common complications.

SINCE THE first cardiac transplant 26 years ago in South Africa by Dr Christian Barnard, newer immunosuppressive agents have changed the long-term outcome and success in all transplant patients. In 1991 approximately 2949 cardiac transplants were performed worldwide and of these, 2125 were performed in the United States. With improved immunosuppression, this population will continue to grow and require close participation of primary care physicians away from the transplant center.

In spite of the improvement in survival, however, there are no universally accepted standards for patient follow-up and management in the postoperative period. Each transplant center has adopted its own patient care and immunosuppression protocols, usually derived by modification of protocol from other centers. Although each center is different, there is a great deal of similarity among centers in long-term management of recipients.

The purpose of this article is to review the general aspects of outpatient follow-up and management of the cardiac transplant recipient, once the patient has left the hospital following the initial transplant procedure. It should provide insight into those aspects of care that can be managed outside a transplantation center, and indicate when to refer patients back to the center for definitive care.

OUTPATIENT FOLLOW-UP

General Aspects. After discharge from the hospital following the transplantation procedure, the patient remains in the transplant center community for several weeks. In the immediate postdischarge period, patients are followed twice weekly for 6 weeks in the Heart Transplant Clinic by the transplant coordinator and physician. During this period the patient is monitored for any evidence of rejection or infection, and ▶

TABLE 1
OUTPATIENT CLINIC SCHEDULE FOR HEART TRANSPLANT RECIPIENTS

Period	Frequency
Weeks 1 through 6	Twice weekly
Months 2 through 4	Monthly
Months 6 and later	Every 3 months

drug levels of immunosuppressive agents are followed. An important aspect of the immediate postdischarge period is the continuation of the patient and family education that was initiated preoperatively during the waiting period. After the initial 6 weeks, patients are followed at preset intervals unless their condition warrants closer monitoring. Before release to the home community, the patients are seen at longer intervals, depending on the patient's biopsy schedule. Table 1 summarizes the Willis Knighton-LSU Medical Center Heart Transplant Clinic outpatient schedule.

Clinic visits routinely consist of physical examination, laboratory studies, drug levels, ECG, chest radiography, echocardiography, and review of endomyocardial biopsies.

Physical Examination. A complete physical examination is performed at each clinic visit, aimed at detecting evidence of infection, cardiovascular dysfunction, renal dysfunction, hypertension, problems with fluid balance, and adverse effects of medication. An accurate weight is recorded at each visit. Vital signs are obtained in supine, sitting, and standing positions. The oropharyngeal cavity is examined for evidence of infection or colonization. Special emphasis is placed on the cardiovascular examination, looking for neck vein distention, pulmonary or peripheral edema, and gallop. The lungs are auscultated for evidence of pulmonary parenchymal or airway disease. The abdomen is examined for hepatosplenomegaly and tenderness. The skin is carefully examined for lesions.

Laboratory Studies. A variety of laboratory tests are obtained on a scheduled basis following transplantation. A CBC with differential white count and platelet count are obtained at each visit. The white count is used to guide dosing of azathioprine. Excessive immunosuppression can be detected by following the hemoglobin and the platelet count. Opportunistic infections which affect the bone marrow may also be suspected from the CBC. A chemistry profile is also obtained at each visit, especially to detect adverse renal or hepatic effects of drug (especially cyclosporin) therapy. Cyclosporin trough levels are measured at each visit and help to guide cyclosporin dosing, especially in the face of renal or hepatic insufficiency.

Serology for Epstein-Barr virus, cytomegalovirus and *Toxoplasma* are obtained weekly for 6 weeks, then monthly until the fourth postoperative month. Surveillance cultures of the throat and urine are obtained weekly for 6 weeks. Blood and urine are cultured for CMV weekly for 6 weeks, then monthly until 4 months. Hepatitis C serology is obtained at 3 months if the donor was HCV positive and the recipient negative.

Lipid profiles are obtained at 3 and 6 months, then subsequently every 6 months. Complete pulmonary function tests and 24-hour creatinine clearance are obtained at 6 months and 1 year, then yearly thereafter.

Electrocardiogram. The ECG was important for the diagnosis of rejection in the precyclosporin era. A drop in summated voltages of the limb leads, V1 and V6 of 20% or more was relatively sensitive for an acute rejection episode. However, the ECG is relatively insensitive in detecting rejection when cyclosporin is part of the immunosuppressant regimen.[1] In these patients, it is perhaps more helpful for identifying rhythm disturbances or detecting asymptomatic myocardial ischemia or infarction. The ECG still remains useful for assessing for rejection in patients who are unable to take cyclosporin, or who have been tapered off of the drug. An ECG is obtained at each clinic visit.

Chest Radiograph. Chest radiography is an important part of the follow-up of cardiac transplant recipients. The lung is the most commonly infected organ, and some pulmonary infections may have an insidious course. Because of this fact and the knowledge that the immunosuppression regimen can mask early signs of infection, the chest radiograph is an important means of identifying pulmonary infections early in the course. We obtain a chest radiograph at every clinic visit for comparison with previous studies and in patients who develop symptoms of upper respiratory or pulmonary infection, even if the physical examination does not yield any positive findings.

Echocardiography. One of the goals in transplantation medicine is to develop noninvasive methods of detecting rejection. Since rejection is associated with impairment of myocardial function, echocardiographic assessment holds some promise for detection

of rejection. Unfortunately, most of the parameters of cardiac function determined by 2-D echocardiography, in particular systolic function, remain within normal limits during episodes of rejection in patients receiving cyclosporin. Although small changes from control values may occur in a given individual during rejection, the value of 2-D echocardiography is limited. Newer approaches involving Doppler echocardiographic determinations, such as isovolumetric relaxation time and pressure half time, are more useful.[2,3]

When present, echocardiographic signs of rejection have a high specificity. However, the degree of abnormality on echocardiography may not correlate with the severity of rejection as determined by endomyocardial biopsy. Response to treatment of rejection can be followed by echocardiography, and failure of the echocardiographic abnormalities to reverse following therapy is a poor prognostic sign. We obtain echocardiographic studies routinely after transplantation. Following discharge from the hospital, 2-D and Doppler echocardiography are performed weekly for 6 weeks. Right ventricular dimensions, left ventricular dimensions and posterior wall thickness, and diastolic properties of the left ventricle by Doppler (isovolumetric relaxation time and pressure half time) are recorded. Since detection of left ventricular dysfunction often occurs later in rejection than can be detected histologically, Doppler echocardiography can supplement but not replace endomyocardial biopsy for detection of early rejection. In particular, the development of diastolic indices of rejection may indicate clinically unsuspected rejection and should prompt for urgent biopsy.

Endomyocardial Biopsy. With widespread use of cyclosporin, the risk of rejection has decreased dramatically; however, there are no reliable clinical signs of rejection. Rejection in the cyclosporin era can only be diagnosed reliably in its early phases by right ventricular endomyocardial biopsy; therefore, these are performed at regular intervals.[4,5,6]

The first biopsy is performed prior to discharge from the hospital, and subsequently once a week for 6 weeks on an outpatient basis. After the first 6 weeks, biopsies are obtained on each clinic visit. If an episode of rejection is identified and treated, follow-up biopsy is performed in 2 to 4 weeks to monitor response to treatment, then according to routine schedule. After the first year, biopsies are performed every 6 months.

If immunosuppression is being tapered, then biopsies are obtained as often as every 3 months.

Outpatient biopsies are performed by transplant cardiologists in the Cardiac Catheterization Laboratory. The right ventricular endocardium is usually approached from the right internal jugular or subclavian vein, and approximately 6 specimens with a bioptome are obtained for histopathologic study. Obtaining a minimum of 4 biopsy samples reduces the chance of missing rejection to 2%. Little information is added by obtaining more than 8 specimens, and the incidence of biopsies of previous sites increases with more than 8 samples per session. The procedure is performed in the morning, with results available within 24 hours. Typically the procedure requires 15 minutes or less. If necessary, the femoral approach can been used, but the risk of infection may be higher.

Endomyocardial biopsy is an uncomfortable but not a painful procedure. Once the importance of the procedure is realized by the patient, his or her cooperation is usually not difficult to obtain, and patients become less apprehensive with time.

TABLE 2
ANTIBIOTIC PROPHYLAXIS REGIMEN FOR OPPORTUNISTIC INFECTIONS

Antibiotic	*Duration*
EVERY PATIENT	
Acyclovir 200 mg bid	2 months
Trimethoprim-sulfamethoxazole DS qd	2 months
Nystatin 200,000 units bid	3 months
TOXOPLASMA SEROLOGIC MISMATCH	
Replace trimethoprim-sulfamethoxazole with Pyrimethamine 50 mg qd	2 months
CMV SEROLOGIC MISMATCH	
Cytogam 150 mg/kg	Within 72 hours
100 mg/kg	at 2, 4, 6 and 8 wks
50 mg/kg	at 12 and 16 wks

MANAGEMENT

Immunosuppression. Prevention of rejection following orthotopic cardiac transplantation is critical. In contrast to kidney transplantation, rejection of the transplanted heart results in death since there are no reliable long-term support systems analogous to renal dialysis for the rejected kidney.

Cyclosporin A has been a major advance in the prevention of allograft rejection. Although the drug does not significantly reduce the number of rejection episodes, it reduces their severity and associated morbidity. It has been proposed that cyclosporin mediates its effects through inhibition of helper T cells, by inhibiting the generation of interleukin 2 and other lymphokines, thereby reducing proliferation of cytotoxic T lymphocytes.[7]

The mainstay of immunosuppression is a triple drug regimen consisting of cyclosporin, azathioprine, and prednisone. Cyclosporin is begun on postoperative day 2 (to allow time for recovery of renal function following transplantation). It is started at a dose of 2 to 4 mg/kg/day in two divided doses, and increased over several days to 8 to 10 mg/kg/day. It is later tapered to approximately 4 mg/kg/day by the end of the first year. In the immediate postoperative period, polyclonal or monoclonal antilymphocyte globulin is given for 4 to 5 days for protection until cyclosporin levels rise. Blood levels are monitored and provide some guidance to dosage adjustments due to alterations in excretion.

Azathioprine is initiated preoperatively and continued postoperatively at 2 to 4 mg/kg/day, tapering over several weeks. The dosage is adjusted to maintain a WBC count of 4 to 6 $\times$ 10^3 cells/μL. Prednisone is begun postoperatively at 1 mg/kg/day, and tapered over 4 weeks to 0.2 mg/kg/day. Further tapering after the first year is attempted if the rejection history permits.

Antimicrobial Prophylaxis. The transplant recipient is subject to a number of opportunistic infections (vide infra). A prophylactic regimen is initiated in all patients, designed to reduce the incidence of infection with cytomegalovirus, *Pneumocystis carinii, Candida* sp, herpes virus, and *Toxoplasma gondii.* This regimen is summarized in Table 2.

Drug Interactions. A number of commonly used drugs can affect metabolism and clearance of the immunosuppressant drugs. Cyclosporin is metabolized by the cytochrome P450 system in the liver, and one of its major side effects is nephrotoxicity. The suppression of the bone marrow by azathioprine can be altered by certain concomitant medications. Some of the better known interactions are given in Table 3.

TABLE 3
COMMONLY USED DRUGS WHICH INTERACT WITH IMMUNOSUPPRESSANT DRUGS

Drug	Effect
AZATHIOPRINE	
Allopurinol	Increases effect of azathioprine
CYCLOSPORIN A	
Substantiated:	
Erythromycin	Increases cyclosporin levels
Ketoconazole	Increases cyclosporin levels
Rifampin	Decreases cyclosporin levels
Phenytoin	Decreases cyclosporin levels
Barbiturates	Decreases cyclosporin levels
Unsubstantiated:	
Aminoglycosides	Increased nephrotoxicity
Amphotericin B	Increased nephrotoxicity
Trimethoprim	Increased nephrotoxicity
Sulfamethoxazole	Increased nephrotoxicity
Cimetidine	Increased Nephrotoxicity
Corticosteroids	Increased cyclosporin levels
Diltiazem	Increased cyclosporin levels
INH	Decreased cyclosporin levels

COMPLICATIONS

Allograft Rejection. Rejection of the transplanted heart is not an uncommon event, but fortunately most of these rejections are mild using the current immunosuppression regimen. The symptoms of rejection are largely nonspecific. The patient may complain of fatigue and malaise. A low grade fever may develop. Physical examination may reveal a fourth heart sound, and the electrocardiogram may demonstrate atrial arrhythmias. A 20% decrease in the summation of the ECG voltages in leads I-III, V1 and V6 may be helpful in diagnosis, but is usually not present when cyclosporin is used for immunosuppression. Since physical findings, electrocardiography, and echocardiography are relatively insensitive, biopsy is performed for confirmation.

Rejection is classified as minimal, mild, moderate, or severe. Minimal rejection features only a few interstitial mononuclear cells. In mild rejection, there is interstitial or perivascular infiltration of mononuclear cells, but no damage to myocytes is detected. Moderate rejection involves limited myocyte damage, and severe rejection involves hemorrhages and extensive neutrophil infiltration and myocyte damage.

During the first 3 months early (mild) rejection is treated with pulse methylprednisone (1 gram IV daily for 3 days). Most episodes respond to this therapy. If the follow-up biopsy does not show improvement, the oral prednisone dose is increased to 1 mg/kg/day then tapered over 2 weeks. After the first 3 months, mild rejection episodes are not treated, but closely monitored. Moderate and severe rejection require more extensive modification of the immunosuppression regimen.

Hypertension. Development of hypertension, primarily diastolic hypertension, is not uncommon following cardiac transplantation. The cause is unclear, but proposed theories include loss of neural control of blood pressure from cyclosporin, sodium and water retention, or enhanced activity of the renin-angiotensin system. Treatment with diuretics and calcium channel blockers is usually sufficient, but angiotensin converting enzyme (ACE) inhibitors or beta blockers may be required. If beta blockers are used, treadmill testing is performed to evaluate tolerance of the drug.

Renal Insufficiency. Another problem which occurs commonly following cardiac transplantation is mild to moderate renal insufficiency. Cyclosporin can impair renal function, perhaps by causing an arteriopathy of the renal arteriole secondary to decreased synthesis of prostacyclin stimulating factor.[8] This would result in renal vasospasm, and may be a major contributor to renal dysfunction in those patients receiving the drug.

Acquired Infections. Infection is a major contributor to mortality and morbidity following cardiac transplantation. Early recognition and management of opportunistic infections is essential, since delay in treatment may result in a fulminant and fatal course. The intracellular microorganisms are of major concern in the immunosuppressed patient.

Current immunosuppression regimens result in depression in polymorphonuclear leukocyte (PMN) function, PMN counts, B-cell function and antibody production, and T-lymphocyte counts and function. The risk of infection with encapsulated bacteria, certain viruses, *Legionella*, mycobacteria, *Listeria*, fungi, and protozoans is increased (Table 4). Infections may result from endogenous organisms, or from organisms acquired from the environment. Another route is reactivation of latent infections, in particular with CMV, ▶

TABLE 4
OPPORTUNISTIC INFECTIONS FOLLOWING CARDIAC TRANSPLANTATION

	Organism	Common sites
BACTERIA		
	Pneumococcus	Lung
	Hemophilus influenza	Lung
	Staphylococcus sp	Lung, soft tissue
	Escherichia coli	Lung
	Klebsiella sp	Lung
	Pseudomonas aeruginosa	Lung
	Legionella pneumophila	Lung
	Listeria monocytogenes	CNS, blood
	Nocardia sp	Lung, CNS
	Mycobacteria sp	Lung
FUNGI		
	Candida	Oral, esophageal, systemic
	Cryptococcus	CNS, lung
	Aspergillus	Lung, CNS
	Coccidioides	Lung, CNS
PROTOZOA		
	Toxoplasma gondii	CNS, liver, heart, eye
	Pneumocystis carinii	Lung
VIRUSES		
	CMV	Lung, liver, retina, systemic
	Herpes simplex	Oral, esophageal, CNS
	Epstein-Barr	Lymphoid tissue
	Varicella-Zoster	Skin, systemic

Epstein-Barr virus, varicella-zoster, tuberculosis, and toxoplasma. A final route, discussed in the next section, is transmission from an infected donor organ to a noninfected recipient.

The most common site of opportunistic infection is the lungs. A less common site, but one associated with greater morbidity, is the CNS. An important feature of infections in the post cardiac transplant patient is that the reduction in PMN counts, PMN function, and macrophage-monocyte function may mask early clinical signs of infection. A high index of suspicion and vigilance must therefore be maintained in the post-transplantation period, and aggressive evaluation and treatment of infectious complications is necessary.

Donor-Transmitted Infections. The transmission of infection through a donor heart to an uninfected recipient can have significant morbidity and mortality. The organisms which can be involved include *Cytomegalovirus* (CMV), *Toxoplasma gondii*, Hepatitis B virus (HBV), and human immunodeficiency virus (HIV).

The most significant route of CMV infection in heart transplant recipients is through the transplanted heart. Donor acquired CMV infection is much more serious than primary CMV acquired from other routes, such as blood transfusion. At present the best means of reducing the impact of CMV infection is to obtain a serologic match between donor and recipient (seropositive donor hearts are transplanted into seropositive recipients, and seronegative hearts into seronegative recipients). The most severe infections occur following transplantation of a seropositive donor into a seronegative recipient. Rapid screening tests now make pretransplantation determination of seropositivity possible.

Most primary infections with *T gondii* in heart transplant recipients are acquired from the organs of donors seropositive for the organism by a recipient who is seronegative. Although pretransplantation serologic screening is not available as it is for CMV, determination of serologic status is obtained at the time of transplantation. Serologic mismatched patients can undergo prophylaxis in the post-transplantation period, and the incidence of *T gondii* infections can therefore be nearly eliminated.

Other infections which can be transmitted via donor organ to the recipient are HIV and Hepatitis B virus. Pretransplantation screening can identify HIV and HBV infection in potential donors, and therefore use of organs from infected donors can be avoided.

Hyperlipidemia. All patients are started on a low cholesterol-low saturated fat diet. We have refrained from routine use of Lovastatin or similar drugs because of a high incidence of rhabdomyolysis when used in conjunction with cyclosporin. All patients with low HDL are encouraged to start exercise programs and work toward weight reduction if indicated. The drug of choice for initial treatment is Lopid 600 mg twice daily. If there is no response to diet and Lopid, Mevacor 20 mg/day is considered. Very close follow-up and monitoring is necessary in either drug regimen.

Interaction of lipids and cyclosporin have important clinical implications. Cyclosporin affects lipoprotein metabolism by raising LDL cholesterol and triglycerides.

Accelerated Coronary Atherosclerosis. The two most important complications limiting survival after transplantation are acute allograft rejection and opportunistic infection. Another important complication which affects allograft recipients later in the postoperative course is the development of occlusive disease of the epicardial coronary arteries. The relatively high incidence of accelerated graft atherosclerosis (AGAS) in post-transplant patients is well known, but the exact pathophysiology is poorly understood. Theories include preoperative or intraoperative immune endothelial damage, abnormal lipid metabolism, perhaps combined with platelet activation. Histologically, the process is characterized by diffuse concentric lesions, causing narrowing of the intimal lumen, and lack of collateral vessels. This remains a major cause of late graft failure in heart transplant recipients. It is estimated that up to 50% of patients develop this type of coronary artery lesion within 5 years after transplantation. Some patients develop coronary artery disease after the first 5 years, and this group generally has less rapid progression.

Prevention is attempted by lowering risk factors, including a low cholesterol and low fat diet, weight reduction if indicated, a regular exercise regimen, control of hypertension, and cessation of cigarette smoking and alcohol consumption. Antiplatelet therapy is often advocated but does not appear to help. The use of cyclosporin does not appear to reduce the incidence of AGAS. One recent study suggests that the calcium channel blocker diltiazem may reduce the progression of the disease, but further study is required.[9]

There may be little warning of the presence of advanced lesions, and sudden death is frequently the presenting sign. The patient does not experience angina since the transplanted heart is denervated. There may be ischemic changes on the ECG, or the development of ventricular arrhythmias or congestive heart failure without evidence of acute allograft rejection.

Treadmill testing is insensitive in detecting the lesion, and coronary angiography is required for diagnosis. We routinely perform right and left heart catheterization on an annual basis. Because of cardiac denervation, heart transplant recipients do not develop angina and may develop silent myocardial infarctions or heart failure. Isolated single coronary artery lesions in the donor heart may be present at the time of transplantation. These isolated lesions can be treated with PTCA, aortocoronary bypass surgery, or retransplantation. Initial success and the restenosis rate in this group appears to be the same as nontransplant patients undergoing PTCA. Unfortunately, the lesion of accelerated graft atherosclerosis is a more diffuse lesion and not amenable to surgical intervention. In advanced stages, the only therapeutic option is retransplantation. ■

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